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SEP 27 2006Remarks/Arguments

Claim 14 has been cancelled without prejudice. Claims 1-12 and 15 are currently pending. No new matter has been added by this amendment. The following discussion addresses the rejections set forth in the Office Action.

Double Patenting Rejection

The Office action states that, on the one hand, certain claims "are" rejected and have been overcome by cancellation of instant claim 13 and filing a terminal disclaimer. It is believed that the Examiner intended to state that the rejections have been overcome by the amendments and the terminal disclaimers and that the rejections have been withdrawn. However, out of caution and to ensure that this is considered a complete response, if Applicant's understanding is not correct and the claims remain rejected, Applicant respectfully traverses for the reasons of record.

Rejection of Claims 1, 14 and 15 Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1, 14 and 15 stating that while being enabling for the process as instantly claimed using macrolide antibiotic, does not reasonably provide enablement for a process using any macrocyclic compound. The Examiner further states the seven Wands factors asserting that the terms macrocyclic compound and catalyst are broad. The Applicant respectfully traverses. While it is true that not all macrocyclic compounds can achieve a bridged macrocyclic, that fact alone does not support a finding that the application lacks enablement. It is believed that the Applicant has provided sufficient guidance for a skilled artisan to apply the process of the invention to any macrocyclic characterized by at least two nucleophilic moieties and determine whether the process was successful and those conditions that are appropriate for carrying out the process without undue experimentation.

The breadth of the claims

The Examiner states that the "term macrocyclic compound and catalyst are broad and are seen to encompass several macrocyclic compounds other than macrolides recited in the instant claim 5." It is agreed by the Examiner that the Applicant has enabled the process of the invention with respect to macrolides characterized by at least two

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nucleophilic moieties. It is believed that such a process can be successfully applied to other macrocyclic systems characterized by at least two nucleophilic moieties. While it is recognized that not all macrocyclic systems can successfully achieve a bridged macrocyclic using the described process, this fact alone does not support the rejection. The Applicant has provided sufficient guidance for a skilled artisan to apply the process of the invention to any macrocyclic characterized by at least two nucleophilic moieties and determine whether the process will be successful. In addition, the terms "macrocyclic compound" and "catalyst" are commonly used in the art of chemistry. A skilled chemist can readily determine those macrocyclics "characterized by at least two nucleophilic moieties" and catalysts which will be successful.

The state of the prior art

The Examiner presented a structure on page 5 of the office action and states that both the oxygen and the nitrogen in the structure with their electron pairs are seen as nucleophilic moieties and that such compound cannot form a bridge with a bridging component as instantly claimed. The Applicant respectfully disagrees. It is assumed that the structure as drawn denotes R₂ as a variable rather than two R groups, to achieve a nucleophilic nitrogen. While it is true that the oxygen atom contains unpaired electrons, it is not considered nucleophilic because the unpaired electrons are delocalized to the imine double bond. Nucleophilicity is not simply defined by the availability of unpaired electrons. Even if it were true that a skilled artisan would consider this compound to be a macrocycle substituted by two nucleophilic moieties and assuming that it were true that the compound (which is likely to be unstable) would not undergo the reaction described in the claim, that fact does not support the rejection. Firstly, it is not seen that the claimed process embraces a process where no bridging reaction occurs. Secondly, it would not require undue experimentation to confirm whether or not a reaction would occur using this compound. Thirdly, the predictability of many theoretical reactions can be achieved with minimal experimentation. Because the function of the claim is to not (1) to define the starting materials to only those compounds where successful reaction is a certainty or (2) to preclude any starting material that is not or will not be successful, the

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fact that the Examiner can identify a compound which, in his opinion, is unlikely to react does not support the rejection.

The level of predictability in the art

The Examiner states that there is insufficient data to substantiate that a bridged product as instantly claimed can be made with any macrocyclic compound comprising two nucleophilic moieties. The Applicant respectfully traverses. It is believed that the Examiner has agreed that the enablement for the process of the invention to macrolide systems characterized by at least two nucleophilic moieties has been met by the Applicant. Macrolide systems are more complex than most macrocyclic systems with two nucleophilic moieties. Therefore, the success of such complex systems allows for predictability of other macrocyclic systems characterized by two nucleophilic moieties as well. The Applicant has provided sufficient guidance for a skilled artisan to apply the process of the invention to any macrocyclic characterized by at least two nucleophilic moieties and determine whether the reaction will be successful. The law does not require the Applicant to ensure that the claims are drafted to ensure that the description of the starting materials explicitly preclude those starting materials which will not be successful.

The amount of direction provided by the inventor

The Examiner states that the instant specification is not seen to provide enough guidance that would allow a skilled artisan to extrapolate from the disclosure and the examples provided to enable the formation of a bridged product as instantly claimed using any macrocyclic compound comprising two nucleophilic moieties. The Applicant respectfully disagrees. Since the enablement for complex macrolide systems has been met, there is no reason to conclude that the instant specification does not provide enough guidance. As stated above, the Applicant has provided sufficient guidance for a skilled artisan to apply the process of the invention to any macrocyclic characterized by at least two nucleophilic moieties. No more is required.

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The existence of working examples

The Examiner states that the working examples set forth in the instant specification are drawn to formation of a bridged product using erythromycin as the macrocyclic compound and that is there is little enabling disclosure for the same process to be extended to any macrocyclic compound. The Applicant respectfully disagrees. The amount of guidance provided in the application is sufficient for one skilled in the art to determine which embodiment conceived, but not yet made, would be inoperative or operative with expenditure of no more than routine effort. The existence of working examples using erythromycin as the macrocyclic compound provides sufficient guidance for a skilled artisan to apply the process to any macrocyclic compounds without undue experimentation. Indeed, this kind of guidance is typical in the art as can be seen by reviewing any standard chemistry textbook.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

The Examiner states that the instant disclosure is not seen to be sufficient to enable the use of any macrocyclic compounds in the process as instantly claimed and that one of ordinary skill in the art would need to carry out the process to determine those macrocyclic compounds and the nucleophilic moieties and catalysts needed to carry out the process. The Applicant respectfully disagrees. While it is true that one of ordinary skill in the art would have to carry out the process in order to confirm which macrocyclic systems will be successful, it would not require undue amount of experimentation to do so. Indeed, the likelihood of success in many instances will be predictable where, for example, highly unstable starting materials are employed. As explained in MPEP 2164.08, claims are not rejected as broader than the enabling disclosure under 35 U.S.C. 112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider them obvious. *In re Skrivan*, 427 F.2d 801, 806, 166 USPQ 85, 88 (CCPA 1970). It is respectfully submitted that such guidance that need not be included are teachings that refer to starting material instability and the like. The guidance as to "how

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to use" the claimed process is set forth in the application and there is expenditure of no more effort than is routinely required in the art to carry out such processes.

As the claims only embrace processes which achieve a bridged macrocyclic product, it is not believed that the claims embrace any inoperative embodiments. However, even if the Examiner were to disagree with this position, the specification is still enabling because undue experimentation is not involved in determining those processes that are successful and operative. *In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). The Applicant respectfully requests that all rejections under 35 U.S.C. §112, first paragraph be withdrawn.

Rejection of Claims 3-12 Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 3-12 stating that the word "derivatives" in claim 3 renders the metes and bounds of the claim unclear. The Examiner further states that the term "substituted" renders the claims in which it appears indefinite in all occurrences where the Applicant fails to articulate by chemical name and structural formula or sufficiently distinct functional language. The Applicant respectfully disagrees. The term "derivative" in claim 3 is directed to compounds that have been derived from erythromycin. The structure of erythromycin and its derivatives are very well known in the art. The patent specification provides substantial guidance as to such compounds. Therefore, it would not be difficult for one of ordinary skilled in the art to determine those compounds that are erythromycin derivatives. With respect to the term "substituted," it is not clear why the Examiner states that the term is unclear. The term "substituted" is further defined in the specification under definition starting on page 10, line 23. Certainly, one could easily determine by visual inspection whether any given moiety is a "substituted alkyl," "substituted aryl" and the like. While it is true that such a term is broad, breadth does not render the claim indefinite. The specification provides substantial guidance as to those substituents that can be used. Indeed, this term has been accepted by the USPTO on numerous occasions, supported by substantially similar specifications. See, for example, US Patent 6,054,435, of record. Applicant respectfully requests that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

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Rejection of Claims 14 and 15 Under 35 U.S.C. §102(b)

The Examiner rejected claims 15 as being anticipated by Or et al (WO 99/21864) stating that Or et al teach a process wherein a macrocyclic compound having at least two nucleophilic groups is treated with a bifunctional bridging $H_2N-(CH_2)_m-A-B-D-X^1$ in the presence of a palladium as catalyst. Applicant respectfully disagrees. WO 99/21864 discloses the use of more than one bridging component to complete the bridge. WO 99/21864 does not disclose or suggest the use of a single bridging component characterized by at least two leaving groups to complete the bridge as is presently claimed. The Examiner additionally rejected claim 14 as being anticipated. The Applicant has cancelled claim 14 without prejudice and therefore rendered the rejection moot. Applicant respectfully requests that all rejections under 35 U.S.C. §102(b) be withdrawn.

Rejection of Claims 1-12 Under 35 U.S.C. §103(a)

The Examiner rejected claims 1-12 as being unpatentable over Or et al (WO 99/21864) stating that one of ordinary skill in the art would be motivated to use the process of the prior art for making a bridged macrocyclic compound using a single bifunctional bridging component since the use of a single bridging component would achieve the said bridging in two steps compared to three steps that the process of Or requires. The Examiner further states that one of ordinary skill in the art would be motivated to extend this to other macrocylics in order to develop new derivatives and that one of ordinary skill in the art would also recognize that the process of making the bridged macrocyclic compound could be extended with a reasonable expectation of success to other derivatives of erythromycin. Applicant respectfully disagrees. It is believed that the Examiner has stated the ultimate goal of every chemist, fewer number of steps to achieve the desired product. However, what one yearns does not translate to what is obvious or what can be achieved. On the contrary, the fact that the present process required fewer steps proved that the process is novel. The process of Or did not describe or suggest the process. Moreover, the process of the present invention results in bridged macrocyclic compounds that differ from the compounds formed by the Or

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process. Therefore one of ordinary skill in the art would not look to or to achieve the process of the present invention. Applicant respectfully requests that the rejection of obviousness be withdrawn.

Conclusion

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

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Dated:

9/27/06